Replacement of the systemic atrioventricular valve with a mechanical prosthesis in children aged less than 6 years: Late clinical results of survival and subsequent replacement

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Objective: We analyzed the survival, clinical course, and role of prosthesis–patient mismatch after systemic atrioventricular valve replacement in children.

Methods: From 1974 to 2006, 69 patients underwent systemic atrioventricular valve replacement (median age 1.2 years, range 1.1 months to 5.4 years), with 17 patients requiring re-replacement of the systemic atrioventricular valve. Prosthesis–patient relationship was analyzed by comparing (1) the prosthetic valve diameter and the predicted annulus diameter based on the body surface area and (2) the prosthetic valve diameter and the measured annulus diameter.

Results: Survival was 73% at 1 year and 65% at 5, 10, and 15 years. Age, weight, body surface area, predicted annulus diameter, prior surgery, underlying disease, and ratio of prosthetic valve diameter to body weight were significant predictors of death. Variables associated with re-replacement of the systemic atrioventricular valve were body surface area, prosthetic valve diameter, predicted annulus diameter, and presence of multiple left-sided obstructive lesions. The majority of patients received a prosthesis larger than the predicted annulus diameter. There was good correlation between the prosthetic valve diameter and the measured annulus diameter ($r = 0.85$). Mismatch, as described by the difference in z scores of prosthetic valve diameter and measured annulus diameter, was not a significant predictor of death or re-replacement of the systemic atrioventricular valve.

Conclusions: Although valve replacement is considered the last therapeutic option after failed attempts of valvuloplasty, long-term outcome is favorable. Selection of the prosthesis is made on the basis of the measured annulus diameter. An elevated ratio of prosthetic valve diameter to body weight is associated with patients with low body weight or a large native annulus in dilated ventricles.

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Valve repair is the treatment of choice in dysfunction of the systemic atrioventricular valve, and refined techniques for both stenotic and regurgitant valves are available.[1] Nonetheless, a subset of patients may still require systemic atrioventricular valve replacement (AVVR) after failed attempts of valvuloplasty.[2] The small size of the native valve annulus, atrium, and ventricle pose problems that are unique in children. Early mortality after AVVR during the first years of life remains high, and the risks of lifelong anticoagulation, subsequent valve replacement, and deterioration of ventricular function have to be taken into account when considering this therapeutic option.[3-6] AVVR can be performed with a bioprosthesis or mechanical prosthesis. Despite the need for lifelong anticoagulation, mechanical valves remain the preferred valves because of their low profile, excellent hemodynamic properties, and durability, and the tendency of bioprostheses to early calcification.[7,8] Patients who require AVVR during early infancy often undergo multiple surgical interventions for a multitude of concomitant lesions,

Abbreviations and Acronyms
AVSD = atrioventricular septal defect
AVVR = atrioventricular valve replacement
BSA = body surface area
MAD = measured annulus diameter
PAD = predicted annulus diameter
PVD = prosthetic valve diameter

making comparison of anatomic and clinical features difficult. Despite the heterogeneity of study groups, risk factors for early death and subsequent valve replacement have been established in previous publications.[3,9,10]

Age and weight at first AVVR and the presence of atrioventricular septal defect (AVSD) or left-sided obstructive lesions have been identified to be related to poor clinical outcome. In addition to the importance of these parameters, several publications have focused on the role of prosthesis–patient mismatch as an important predictor for patient outcome.[3,11] In this study we report on our experience with AVVR with special emphasis on the role of prosthesis–patient mismatch.

Materials and Methods

Patients

Patients who underwent AVVR with a mechanical prosthesis between 1974 and 2006 at our institution were identified from a computerized database. Patient charts, catheterization records, and operative data were studied retrospectively. Collected data included age, weight, and body surface area (BSA) at AVVR, diagnosis, number of operations and surgical valvuloplasties before AVVR, and type and size of prosthesis. Five patients underwent AVVR with a bioprosthesis before mechanical AVVR. Those patients were included in the study group when the bioprosthesis was replaced by a mechanical valve within the first 6 years of life. Patients were followed until the time of last clinical visit or death. Follow-up was complete in all patients. The study was approved by the institutional research ethics board.

Statistical Analysis

Analysis of data was performed with the Statistical Package for the Social Sciences Version 14.0 (SPSS Inc, Chicago, Ill). Data are reported as frequencies and median with ranges. Curves for survival and freedom from repeated AVVR were obtained by the Kaplan–Meier method. Predictors of time to the event of death or subsequent AVVR (re-AVVR) were studied by a log-rank test for categoric variables and a Cox regression model with univariate and age-adjusted multivariate analysis for continuous variables.

Measurement of Atrioventricular Valve Size

The predicted annulus diameter (PAD) was calculated on the basis of the patients' BSA.[12] Measured annulus diameter (MAD) was assessed by echocardiography in the 4-chamber view from hinge point to hinge point in 43 patients before surgical intervention. In 8 patients in whom echocardiography was not available, assessment of MAD was done on angiography. The z score of the patients' MAD was calculated as described by Daubeney and colleagues.[12] In the same way, we calculated the z score of the prosthetic valve diameter (PVD). The degree of prosthesis–patient mismatch was defined as the difference between the z score of PVD and the z score of the MAD as previously described.[11] The presence of stenosis or regurgitation was estimated by color Doppler and pulsed-wave Doppler.

TABLE 1. Patient characteristics at initial atrioventricular valve replacement

Age at first AVVR	1.2 y (0.09–5.4)
Weight at first AVVR	7.1 kg (3.2–16.7)
BSA	0.38 m^2 (0.20–0.72)
PVD	19 mm (15–29)
Prosthesis/weight ratio	2.5 mm/kg (1.2–5.1)
PAD	16.7 mm (12.4–20.5)
MAD*	19 mm (11–40)
Z score MAD*	1.2 (−3.8–+8.11)
Follow-up	3.4 y (0.6–28.4)
Regurgitation	n = 37 (54%)
Stenosis	n = 20 (29%)
Combined lesion	n = 12 (17%)
Cardiac defect	
AVSD	n = 22 (32%)
Left-sided obstructions	n = 16 (23%)
"Isolated" valve anomaly	n = 17 (25%)
Univentricular heart	n = 8 (11%)
Other cardiac defects	n = 6 (9%)
Prosthesis type	
Carbomedics (Austin, Tex)	n = 33 (48%)
St Jude Medical (St Paul, Minn)	n = 26 (38%)
Björk Shiley (Irvine, Calif)	n = 5 (7%)
American Thoracic Society (New York, NY)	n = 4 (6%)
Omnicarbon (Inver Grove Heights, Minn)	n = 1 (1%)

AVVR, Atrioventricular valve replacement; *BSA,* body surface area; *PVD,* prosthetic valve diameter; *PAD,* predicted annulus diameter; *AVSD,* atrioventricular septal defect; *MAD,* measured annulus diameter. *Measurement was available in 51 of 69 patients (74%).

Results

Patient Characteristics

A total of 88 mechanical AVVRs were performed in 69 patients (34 male, 35 female), with 17 patients requiring re-AVVR and 2 patients requiring a third AVVR (re-re-AVVR). Congenital heart disease was the underlying cause for valve replacement in all patients. Of the 61 patients with biventricular circulation, 59 patients had a left systemic ventricle and replacement of the mitral valve and 2 patients had a right systemic ventricle and replacement of the tricuspid valve. In 8 patients with functionally univentricular hearts, 6 patients had replacement of the tricuspid valve and 2 patients had replacement of the mitral valve. Patient characteristics and age distribution are summarized in Table 1 and Figure 1.

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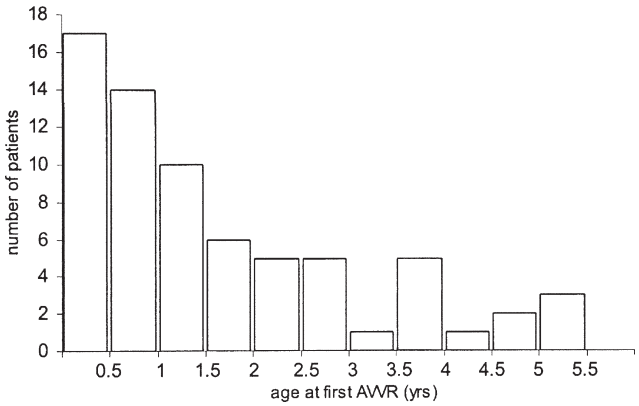

Figure 1. Age distribution of patients (n = 69) at time of first AVVR. *AVVR,* Atrioventricular valve replacement.

A total of 85 operations were performed in 53 patients (77%) before first AVVR, including 37 valvuloplasties of the systemic atrioventricular valve in 32 patients (46%, including repair of AVSD) and 5 valve replacements with a bioprosthesis in 5 patients (7%). In 17 patients (25%) concomitant surgery was performed at the time of AVVR. In 2 patients the prosthesis was placed in a supra-annular position because of the small dimension of the native annulus. All patients were placed on oral anticoagulation therapy with phenprocoumon or warfarin sodium, aiming at an international normalized ratio between 2.5 and 3.5.

Survival and Predictors of Death

Survival for the entire cohort was 73% at 1 year and 65% at 5, 10, and 15 years. Among the total of 22 deaths, 20 patients died after first AVVR and 2 patients died after re-AVVR; 8 of 20 deaths after first AVVR occurred within 30 days after operation (early mortality 11%). The 2 patients who died after re-AVVR had urgent re-AVVR for acute valve thrombosis (1 intraoperative death, 1 death 3 months after re-AVVR).

Univariate analysis of survival revealed age, weight, BSA, PAD, ratio of PVD to body weight at first AVVR, prior surgery, presence of AVSD, and functionally univentricular heart to be predictors of death. The presence of isolated valve disease was associated with a significantly better survival (Table 2, Figure 2). Whereas an elevated ratio of PVD to body weight was associated with poor outcome, the *z* score difference as a measure for prosthesis–patient mismatch did not reach statistical significance. Age-adjusted multivariate analysis showed significant difference for the ratio of PVD to body weight and the presence of AVSD. Survival in the presence of isolated valve anomaly was significantly better.

Complications

Complications in the survivors included complete atrioventricular block requiring pacemaker implantation in 7 patients (11%, 6 patients after first AVVR, 1 patient after re-AVVR). Major hemolysis did not develop in any patient.

TABLE 2. Comparison between survivors and nonsurvivors

	Survivors n = 47	Nonsurvivors n = 22	*P* univariate	*P* multivariate
Age at first AVVR	1.4 y (1.1 mo–5.4 y)	0.7 y (2.3 mo–3.7 y)	.048	
Weight at first AVVR	8.1 kg (4.1–16.7)	5.6 kg (3.2–14.2)	.024	.32
Body surface	0.40 m^2 (0.23–0.72)	0.30 m^2 (0.2–0.65)	.018	.21
Prior surgery	33	20	.04	.06
Prior valvuloplasty	20	12	.35	.27
Concomitant surgery	13	4	.24	.08
PVD	17 mm (16–29)	19 mm (15–23)	.426	.43
Prosthesis/weight ratio	2.3 mm/kg (1.2–4.5)	3.5 mm/kg (1.6–5.2)	.001	.02
PAD	17.1 mm (13.2–22.5)	15.1 mm (12.4–21.5)	.014	.17
MAD*	19.2 mm (12–40)	15.5 mm (11–35)	.234	.52
z score difference*				
>1 ("oversized")	7/38 (18%)	4/13 (31%)	.35	.38
>−1 <1 ("matched")	17/38 (45%)	5/13 (38%)	.75	.73
<−1 ("undersized")	14/38 (37%)	4/13 (31%)	.09	.08
Cardiac defect				
AVSD	12	10	.039	.05
Left-sided obstructions	12	4	.36	.45
Isolated valve anomaly	15	2	.035	.05
Univentricular heart	3	5	.037	.16
Other cardiac defects	5	1	.55	.73

AVVR, Atrioventricular valve replacement; *PVD,* prosthetic valve diameter; *PAD,* predicted annulus diameter; *MAD,* measured annulus diameter; *AVSD,* atrioventricular septal defect. *Measurement was available in 51 of 69 patients (74%).

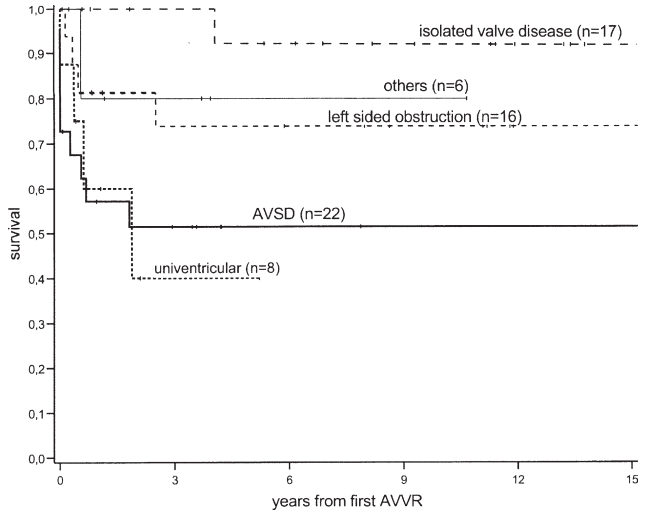

Figure 2. Survival for diagnosis-related groups (n = 69). *AVSD,* Atrioventricular septal defect; *AVVR,* atrioventricular valve replacement.

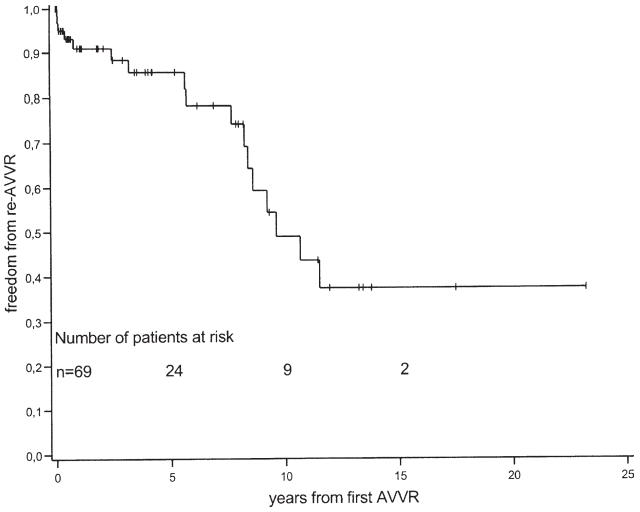

Figure 3. Freedom from re-AVVR. *AVVR,* Atrioventricular valve replacement.

Although small paravalvular leaks occurred occasionally, no patient required reoperation for this reason. Fatal intracranial hemorrhage occurred in 1 infant at the age of 18 months in the presence of an international normalized ratio greater than the normal range. Seven patients had acute valve dysfunction because of prosthetic valve thrombosis or leaflet entrapment by pannus formation requiring re-AVVR. Hemiparesis developed in 1 patient shortly after AVVR, but symptoms resolved entirely. One patient had intermittent atrial fibrillation at the age of 15 years, 11 years after the first AVVR. Replacement of the prosthetic valve was performed because the transprosthetic gradient and systolic pulmonary artery pressure were elevated, but atrial fibrillation recurred. This patient had successful ablation of his arrhythmia and is currently in sinus rhythm. No case of prosthetic valve endocarditis occurred.

Indication, Timing, and Risk Factors for Subsequent Replacement of the Systemic Atrioventricular Valve

Of 88 AVVRs, 19 were subsequent AVVRs with 17 re-AVVRs and 2 re-re-AVVRs (median age at initial AVVR 1.2 years, range 1.1 months to 5.4 years). Freedom from re-AVVR for the entire cohort was 91% at 1 year, 86% at 5 years, 49% at 10 years, and 37% at 15 years from first AVVR (Figure 3). Mechanical valves were used for all re-AVVRs. Freedom from re-AVVR was characterized by a small but steady number of early replacements during the first years and a steep decrease at 7 to 10 years after the initial AVVR. Indications for subsequent AVVR were acute dysfunction caused by valve thrombosis or leaflet entrapment by pannus formation in 7 patients and progressive stenosis caused by patient growth in 12 patients. Three patients with acute valve thrombosis received thrombolytic therapy, but all still required re-AVVR. Re-AVVR was performed at an interval of 5.7 years (range 1 month to 10.7 years) from the first AVVR at an age of 6.5 years (range 2 months to 16.1 years). At this point, body weight had increased from 6.7 kg (range 4.1–16.7 kg) to 16.9 kg (range 4.1–57.3 kg). The diastolic mean gradient across the mechanical valve on echocardiography was 14 mm Hg (range 10–18), and all but 1 patient had elevated systolic pulmonary artery pressure as assessed by catheterization before re-AVVR (median 53 mm Hg, range 25–84 mm Hg).

The PVD of the initially implanted valve was 17 mm (range 15–29 mm), and the PVD of the newly implanted valve was 21 mm (range 16–31 mm). In all patients who underwent re-AVVR for progressive stenosis caused by patient growth, a prosthesis larger than the initial prosthesis could be implanted. Average valve size increase in all 17 patients was 3 mm (range 0–8 mm).

For the analysis of predictors of re-AVVR, we included all survivors of first AVVR (n = 49) to compare patients requiring re-AVVR (n = 17) with patients who did not (n = 32). BSA, PVD, PAD, and the presence of multiple left-sided obstructive lesions were associated with a higher risk for re-AVVR.

Prosthesis–Patient Relationship

Assessment of the MAD before AVVR was available in 51 of 69 patients (74%). The median PAD for these patients was 16.7 mm (range 12.4–22.5 mm). The median MAD was 19 mm (range 11–40 mm) with a median *z* score of 1.2 (range −3.8 to +8.11), and the median PVD was 19 mm

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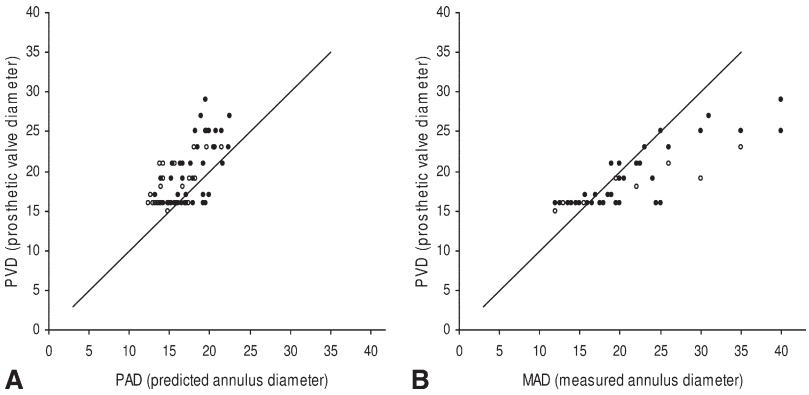

Figure 4. A, Relationship between PVD and PAD. The majority of patients received a prosthesis with a PVD larger than the PAD (*points above the line*). B, Relationship between PVD and MAD. PVD = MAD (*line*). Survivors (*closed circles*) and nonsurvivors (*open circles*). *PVD,* Prosthetic valve diameter; *PAD,* predicted annulus diameter; *MAD,* measured annulus diameter.

(range 15–29) with a median z score of 1.44 (range −2.17 to +4.61).

Figure 4, *A* and *B*, shows the relationship between PVD and PAD and the relationship between PVD and MAD. As shown in Figure 4, *A*, the majority of patients received a prosthesis that was larger than the PAD, and there was only poor correlation between these 2 parameters ($r = 0.62$). When comparing the PVD and the MAD (Figure 4, *B*), we found good correlation between these 2 parameters ($r = 0.85$).

Prosthesis–patient mismatch was defined as the difference between z scores of PVD and MAD. The median z score difference (z score PVD − z score MAD) was −0.51 (range −5.13 to +3.14). As proposed by Eble and colleagues,[11] "oversizing" of the prosthetic valve was noted to be present when the z score difference was greater than 1. "Undersizing" was present when the difference was less than −1 (Figure 5). Because the smallest available prosthesis had a diameter of 16 mm (only one 15-mm prosthesis was used), "oversizing" was present in 11 patients (21%) with a MAD less than 19 mm. "Undersizing" was present in 18 patients (35%), and data were skewed to patients with a large MAD. Mismatch, defined on this basis, did not reach significant difference between survivors and nonsurvivors (Table 2) and between patients requiring re-AVVR and patients who did not.

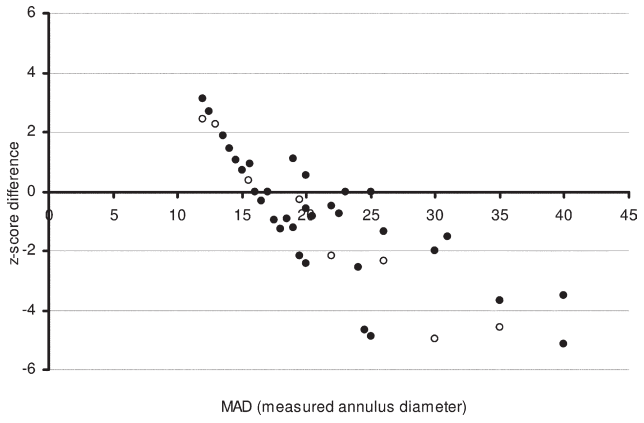

Figure 5. *Z* score difference (z score PVD − z score MAD) as a measure of geometric disparity in relation to MAD. Survivors (*closed circles*) and nonsurvivors (*open circles*). *MAD,* Measured annulus diameter.

Discussion

To our knowledge, the present report is the largest single-center study on AVVR during the first years of life, whereas most single-center studies refer to a limited number of patients despite inclusion of patients up to 18 years old.[4,6,9]

Survival Analysis

Early mortality was 11% in this study, which is comparable to other reports in which early mortality after initial AVVR ranges from 11% to 20%.[4,6,10] Early mortality after valve replacement during the first 2 years of life is reported to be even higher. In our series, 30-day mortality in children aged less than 2 years was 13%. Other authors reported an early mortality of 36% and 52% in this subgroup,[4,13] but there are also reports of small series with an early mortality of 14% to 20%.[9,10,14] After hospital discharge, there are few deaths and long-term survival is favorable with only a moderate impairment in general health status for school-aged children and a near-normal quality of life for the majority of adolescents and young adults.[15] Long-term survival in our series was somewhat lower than that reported by other authors,[3,4,9] which is likely because we included children aged less than 6 years and a relatively high proportion of patients with functionally univentricular hearts, who are known to be high-risk patients.

Despite the dramatic progress in intraoperative management and postoperative care, and a study time of 32 years, we were not able to assess statistically significant improvement in survival over time. This may be attributable to the heterogeneity of the study group with a broad spectrum of underlying cardiac diseases. Nonetheless, Alexiou and colleagues[9] showed a decrease in operative mortality from

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31% before 1990 to 3.6% after 1990. In addition to the role of age, weight, BSA, PAD, ratio of PVD to body weight, and diagnosis for survival, as shown in other studies,[3,12,16] we found prior surgery to be related with higher mortality.

Subsequent Valve Replacement

Re-AVVR is almost inevitable in children. Ten-year freedom from re-AVVR was 49% in this study, meaning that approximately half of the survivors require subsequent AVVR within 10 years. This is comparable to other studies in which 10-year freedom from re-AVVR was 56%.[6,17] Biologic valves show rapid deterioration with time and sometimes need to be replaced within months.[8] Therefore, we only use biologic valves occasionally when proper management of anticoagulation is not ensured. The two main indications for re-AVVR after mechanical AVVR were progressive stenosis caused by patient growth and acute dysfunction caused by thrombosis or leaflet entrapment by pannus formation, whereas prosthetic valve endocarditis, paravalvular leak, regurgitation, and left ventricular outflow tract obstruction were not encountered in our series. A multi-institutional study from the Pediatric Cardiac Care Consortium[18] showed that the need for re-AVVR highly depends on the prosthesis size and the patient's age at initial AVVR. When 10-year freedom from re-AVVR is compared, the fact of inclusion of patients up to 18 years old[4,19] has to be taken into account.

A matter of concern is the timing of re-AVVR. Whereas the indication for re-AVVR is not debatable in acute dysfunction after a failed attempt of thrombolysis in valve thrombosis, re-AVVR for progressive stenosis is less clearly defined. Cardiac catheterization was proposed once the maximum transprosthesis flow velocity exceeds 270 cm/s.[17] At our institution we opt for cardiac catheterization as soon as there are signs of elevated right ventricular pressure on echocardiography, in addition to a mean transprosthetic gradient greater than 12 mm Hg. An increase in BSA[20] or body weight[21] of approximately 2 or 2.5 times of that at initial implantation is not suitable for timing, because no significant difference in rate of weight gain among patients who required subsequent AVVR and patients who did not was observed.[18]

In all of our patients with re-AVVR for progressive stenosis, the new valve could be upsized. Although "fixing" of the native valve annulus to the sewing ring of the prosthetic valve was considered to hinder further growth of the native annulus, all studies reporting on subsequent AVVR showed a sufficient gain in prosthesis size at re-AVVR,[10,18,19,22] suggesting that there is persisting annular growth.

Mortality after subsequent AVVR is low.[18] In our series there were only 2 deaths after re-AVVR. Re-AVVR was performed in the presence of an acutely thrombosed valve in both patients, and both patients were in poor clinical condition.

Prosthesis–Patient Mismatch

Prior studies have focused on the role of an increased ratio of PVD to body weight as a predictor of adverse outcome.[3] The majority of our patients received a prosthesis that was larger than the predicted annulus size, resulting in an elevated ratio of PVD to body weight. These patients represent, at least in part, 2 subsets of patients: (1) small children with low body weight in whom selection of a "too-large" prosthesis was inevitable because of the lack of smaller prosthesis and (2) patients in whom a smaller prosthesis would have been available but was not implanted because of large annulus dimensions in highly dilated ventricles or patients with univentricular hearts. Selection of a prosthesis larger than the PAD was not made for the incentive to avoid patient outgrowth but to implant a prosthesis that fitted the actual size of the annulus as shown by the relationship between PVD and MAD. In dilated ventricles with a large MAD, the PVD tended to be even smaller than the MAD, and in these patients a prosthetic valve was chosen as close to the PAD as possible. We suggest that the association of an elevated ratio of PVD to body weight with high mortality reflects selection of a high-risk cohort, including very small infants in whom early surgery is mandatory because of the complexity of the underlying disease or poor clinical condition and patients with a large annulus in a highly dilated ventricle with poor ventricular function, which was shown to be related to higher mortality.[11]

For this reason we believe the use of the z score difference, as previously described,[11] is a more suitable parameter to analyze prosthesis–patient mismatch than the ratio of PVD to body weight. In contrast with the study of Eble and colleagues,[11] differences in survival or need for re-AVVR between patients with a "matched," "oversized," or "undersized" prosthetic valve in relation to the measured annulus did not reach statistical difference.

Limitations

We acknowledge that the lack of clinical data reflecting the clinical status of the patient at AVVR is an important drawback of this report when discussing operative mortality. We think that this aspect is especially important in infants requiring valve surgery during the first year of life. This is a retrospective study, rendering complete data collecting difficult. Advancement in operative and perioperative care may have affected outcome, although we were not able to detect this. The inclusion of patients with univentricular hearts, who have a large ventricle and therefore a large native annulus, makes the calculation of the PAD problematic. Because we focused on the relationship be-

tween the MAD and the PVD, this fact did not lead to misinterpretation of data.

Conclusions

This study shows that selection of prosthesis in systemic AVVR in small children is made on MAD rather than PAD. Despite the simplicity of the prosthesis/weight ratio and its association with increased mortality, this parameter does not compellingly reflect geometric disparity between the prosthesis and the cardiac dimensions. There is a need to place smaller prosthetic valves at the surgeon's disposal even if their use will be restrained to a limited portion of patients. Although approximately half of the survivors require subsequent AVVR within 10 years, the operative risk of re-AVVR is low. At the time of re-AVVR, the new valve can be upsized. AVVR should be considered as a promising therapeutic option after failed attempts of valvuloplasty and should be undertaken as long as the patient is in stable clinical condition.

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